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Protecting Research Subjects -- What Must Be Done

As we race toward the as yet unimagined scientific and medical triumphs of the 21st century, no one is more hopeful about the journey than I am. Nevertheless, moving ahead with cutting-edge research must not mean leaving behind well-established international standards for protecting human subjects in clinical trials. None of these principles is more important than the protection of research subjects by informed consent based on full disclosure of potential risks and benefits.

I did not expect, or want, to complete my tenure as secretary of health and human services by raising questions about the safety of patients in clinical research. However, recent developments leave me little choice. Much brilliant biomedical research is being done in universities and academic health centers, and the federal government supports a substantial portion of this research. So we have a responsibility to make sure the money we invest -- money that comes from U.S. taxpayers -- is not used in ways that harm people participating in clinical trials or that unnecessarily risk harming them.

The vast majority of government-supported studies adhere to strict protocols and the highest ethical standards. But even one lapse is one too many. The American people expect that clinical researchers will never compromise or neglect the safety of human subjects. The moral and ethical reasons for paying heed to this demand require no explanation. However, there are also practical reasons. To put it simply, if we cannot guarantee sound research in general -- and patients' safety in particular -- public support for gene therapy and other potentially lifesaving treatments will evaporate. Volunteers will not show up, and the generous stream of research dollars that Congress and President Bill Clinton have provided in recent years may shrink. So clinical researchers and the institutions that support them must, without exception, maintain the public's confidence in our work, our competence, and most important, our ethics.

Unfortunately, the public's confidence in all three has been seriously shaken by the death of 18-year-old Jesse Gelsinger in a gene-transfer trial at the University of Pennsylvania in which human subjects were not adequately protected and which presented the appearance of substantial financial conflicts of interest. Moreover, this young man's death led to the discovery by the National Institutes of Health (NIH) of many hundreds of unreported adverse events among volunteers enrolled in gene-transfer experiments. The failures to report adverse events properly to the NIH occurred despite the compliance of the gene-therapy researchers with Food and Drug Administration (FDA) reporting requirements.

The medical and research communities, including institutional review boards (IRBs), agree with the Department of Health and Human Services that this appalling state of affairs is unacceptable.

We cannot tolerate or excuse inadequacies in our system of protection for human research subjects. In a letter sent on May 30 to the leaders of major research universities, I wrote that the ultimate responsibility for protecting human subjects must be borne by the institutions that perform the research. I applaud the Association of American Universities, which represents 61 institutions of higher education, for echoing this sentiment in its recently released report on the protection of human subjects. (1) The association understands that, regardless of government actions, research subjects will not be better protected unless research institutions take their responsibilities seriously.

To ensure maximal protection, research institutions may need to undertake remedial action. Although in the short run such action may entail substantial costs, research awards from the federal government and other sponsors already provide revenue that can be used to help fix problems. As a former chancellor of the University of Wisconsin in Madison, I know firsthand the nearly unlimited demands that can legitimately be made on limited resources. Nevertheless, no priority in research is more important than the protection of subjects. Therefore, we must determine the true costs of an exemplary system of protection and ensure that adequate resources are made available.

The need to strengthen protections for human subjects is rooted in four recent trends in clinical research. First, researchers may not be doing enough to ensure that subjects fully understand all the potential risks and benefits of a clinical trial. Full disclosure is a necessary precondition to free choice. Accordingly, subjects who do not understand the potential risks of a trial cannot be said to have chosen freely to face those risks.

In a report released in February by the Office of the Inspector General of the Department of Health and Human Services, (2) disturbing recruitment practices were brought to my attention, including the case of a woman in a nursing home who was allegedly forced to participate in a study under threat of expulsion from the home. The report focused on studies funded by drug companies, which sponsor most clinical research. It noted that aggressive recruiting by researchers who have been offered money or other inducements may be contributing to the erosion of informed consent. As researchers are pressured to recruit subjects quickly in order to discover the next blockbuster drug, they may misrepresent the true nature of a trial, or they may simply appeal to their patients' trust. The report also described misleading promotions and advertisements. Researchers promised treatment for disease, when in fact they wanted to use patients in trials of drugs that were potentially both risky and ineffective. Neither for financial reasons nor under the guise of furthering science can we allow any erosion of informed consent. To use human subjects without their full knowledge and understanding, to place them at needless risk, is unconscionable.

Second, too many researchers are not adhering to standards of good clinical practice. The FDA has identified cases in which researchers failed to disqualify subjects who did not meet the criteria for a study, failed to report adverse events as required, failed to ensure that a protocol was followed, and failed to ensure that study staff had adequate training. (3) These were not isolated incidents on the fringes of science. Instead, these troubling problems occurred at some of our most prestigious research centers and involved leaders in their fields of study. There can be no shortcuts when it comes to the protection of human subjects. Good clinical practices are neither esoteric nor frivolous. When adverse events are properly reported, the FDA and other bodies charged with the oversight of research can assess the safety of a particular study, as well as similar studies, and look for trends. In that way, subjects are better protected.

Third, IRBs, the key element of the system to protect research subjects, are under increasing strain. In June 1998, the Office of Inspector General of the Department of Health and Human Services issued four investigative reports, which indicated that IRBs have excessive workloads and inadequate resources. (4,5,6,7) At a number of institutions, IRB oversight was inadequate, and on occasion, researchers were not providing the boards with sufficient information for them to evaluate clinical trials fully.

Although, as noted in a subsequent report this year, important steps have been taken to remedy problems, (8) more progress is needed. Findings from the Office for Protection from Research Risks (OPRR) of the NIH and from the FDA only reinforce the primary conclusion of the inspector general's report -- that IRBs are under considerable pressure and that the protection of human research subjects must be strengthened. Although we all have a stake in enhancing the IRBs, ultimately this responsibility must fall on the leaders of our research universities and academic medical centers.

Fourth, the nature of the clinical trials themselves is changing. More and more, potential conflicts of interest and ethical dilemmas arise, as academic researchers serve as both investigators and sponsors or patent holders of products. In her editorial entitled "Is Academic Medicine for Sale?" Angell warned against this blurring of boundaries between industry and academic medicine. (9) I believe she is correct in arguing that close collaboration between a company and a researcher creates goodwill on the part of the researcher that can lead to a conflict of interest, since the researcher's self-interest may subtly influence his or her scientific judgment.

All four of these trends in clinical research are disturbing. Any deterioration in the protective foundation we have laid can cause direct harm to human subjects of research and indirect harm to the reputations of the investigators, their academic institutions, and the entire research community. Moreover, if we are to keep testing new medicines and new approaches to curing disease, we cannot compromise the trust and willingness of patients to participate in clinical trials.

Given this state of affairs, the federal government, researchers, and research institutions must come together with a sense of urgency to reform the current system of protections so that it functions smoothly and ensures maximal protection for all human subjects. We are already working to strengthen and improve the system. In March, my department announced that sponsors of gene-transfer research are required to submit monitoring plans routinely in advance to the FDA and that the NIH and the FDA have initiated a series of symposiums on gene-transfer safety. On May 23, to complement these initiatives and to address the inadequacies in research protections, I announced several additional steps to improve the safety of subjects in clinical trials; strengthen government oversight of medical research, including gene-transfer research; and reinforce clinical researchers' responsibility to follow federal guidelines.

First, the NIH and the FDA will undertake an aggressive effort to improve education and training. The objective is to ensure that all clinical researchers, research administrators, IRB members, and IRB staff receive appropriate training in bioethics and other issues related to research involving human subjects. This training will be required for all clinical investigators who receive NIH funds and will be a prerequisite to the receipt of all NIH grants.

Second, the NIH and the FDA will issue specific guidelines on informed consent, reaffirming the expectation that research institutions and sponsors will audit records for evidence of full

compliance. The new guidelines will also reassert the obligation of investigators to confirm the informed consent of participants when any serious trial-related event occurs that might affect a subject's willingness to participate.

Third, in order to improve monitoring, the NIH will now require investigators who are conducting small-scale early clinical trials (phase 1 and phase 2 trials) to submit monitoring plans at the time they submit their grant applications. Researchers will be expected to share these plans with the IRBs. In addition, the FDA will soon issue new guidelines for data and safety monitoring boards (DSMBs). These guidelines will specify the relationship between DSMBs and IRBs and will define the circumstances under which DSMBs should be required. They will also cover membership of the DSMBs, as well as how they should operate, their responsibilities, and their obligations to maintain patients' confidentiality.

Fourth, we will issue additional documents to clarify regulations relating to conflicts of interest. To ensure that research subjects are appropriately informed and that research results are analyzed and presented objectively, the Department of Health and Human Services will hold public discussions with universities and academic medical centers to find new ways to minimize or eliminate conflicts of interest. On the basis of these public forums, the NIH, the FDA, and other agencies will work together to develop the new guidelines.

Fifth, we will pursue legislation to enable the FDA to levy civil monetary penalties for violations of informed consent and other important research practices. The fines would be up to \$250,000 per clinical investigator and up to \$1 million per research institution. Financial penalties and administrative actions will give the agency a wider range of tools for use in disciplining researchers, sponsors, and institutions that do not follow federal guidelines. As an interim step, the NIH, the FDA, and other agencies will work more closely together to identify problems and enforce regulations.

Along with these measures, the role of the OPRR is being expanded. Its responsibilities have been transferred to the Office of the Secretary, and it has been renamed the Office for Human Research Protections. This new office will assume the function of protecting human research subjects. We look to it for leadership in articulating our goals for protecting persons who volunteer to participate in research. The new office will also provide leadership for all 17 federal agencies that carry out research involving human subjects. Dr. Edward Greg Koski, associate professor of anesthesia at Harvard Medical School and director of human research affairs for a consortium of medical institutions, was named the first director of the new office. Koski is a national leader in ensuring that people taking part in research are better protected and fully informed.

As I have noted, adequately protecting human research subjects can never be a job for government alone. All of us -- investigators, practicing physicians, and academics -- want sound clinical research. The never-ending challenge for academic institutions and other organizations participating in research is to make sure that researchers and other personnel have up-to-date training and a thorough knowledge of their responsibilities. Those responsibilities include communicating with IRBs, ensuring that procedures for informed consent are followed, monitoring compliance with protocols, and reporting on safety issues.

My challenge to leaders of academic medical centers, university presidents, and everyone else

involved in the oversight of clinical research is to take the responsibility, and the necessary actions, to strengthen the conduct of research at their institutions. This means taking a critical look at the mechanisms for the oversight of clinical trials, partnerships with the private sector, and ethical guidelines at each institution. It also means allocating appropriate funding for the protection of human subjects. Above all, it means providing IRBs and other institutional bodies with the stature, authority, and resources they need to do their jobs.

The tragic death of Jesse Gelsinger focused national attention on the inadequacies in the current system of protections for human research subjects. Although these inadequacies must be strongly censured, they can also serve as a catalyst for change and improvement in clinical research. With renewed determination, we must work together to reform the current system so that it operates more effectively, so that it can more quickly respond to new trends in clinical research, and above all, so that it can guarantee the greatest possible protection for every human subject, in every clinical trial and at every research institution in the country. We have been the beneficiaries of an extraordinary golden age of biomedical research. We want that research to continue to flourish and make this a century of scientific discovery and progress.

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I am indebted to Dr. Jane Henney and Dr. Ruth Kirschstein for their contributions to this article.

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